Surgical treatment of fibroids for subfertility

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[Intervention Review]

Surgical treatment of fibroids for subfertility

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ABSTRACT

Background

Fibroids are the most common benign tumours of the female genital tract and are associated with numerous clinical problems including a possible negative impact on fertility. In women requesting preservation of fertility, fibroids can be surgically removed (myomectomy) by laparotomy, laparoscopically or hysteroscopically depending on the size, site and type of fibroid. Myomectomy is however a procedure that is not without risk and can result in serious complications. It is therefore essential to determine whether such a procedure can result in an improvement in fertility and, if so, to then determine the ideal surgical approach.

Objectives

To examine the effect of myomectomy on fertility outcomes and to compare different surgical approaches.

Search methods

We searched the Cochrane Gynaecology and Fertility Group (CGFG) Specialised Register, CENTRAL, MEDLINE, Embase, PsycINFO, CINAHL, Epistemonikos database, World Health Organization (WHO) International Clinical Trials Registry Platform search portal, Database of Abstracts of Reviews of Effects (DARE), LILACS, conference abstracts on the ISI Web of Knowledge, OpenSigle for grey literature from Europe, and reference list of relevant papers. The final search was in February 2019.

Selection criteria

Randomised controlled trials (RCTs) examining the effect of myomectomy compared to no intervention or where different surgical approaches are compared regarding the effect on fertility outcomes in a group of infertile women suffering from uterine fibroids.

Data collection and analysis

Data collection and analysis were conducted in accordance with the procedure suggested in the *Cochrane Handbook for Systematic Reviews of Interventions*.

Main results

This review included four RCTs with 442 participants. The evidence was very low-quality with the main limitations being due to serious imprecision, inconsistency and indirectness.

Myomectomy versus no intervention

One study examined the effect of myomectomy compared to no intervention on reproductive outcomes. We are uncertain whether myomectomy improves clinical pregnancy rate for intramural (odds ratio (OR) 1.88, 95% confidence interval (CI) 0.57 to 6.14; 45 participants; one study; very low-quality evidence), submucous (OR 2.04, 95% CI 0.62 to 6.66; 52 participants; one study; very low-quality evidence), intramural/subserous (OR 2.00, 95% CI 0.40 to 10.09; 31 participants; one study; very low-quality evidence) or intramural/submucous fibroids (OR 3.24, 95% CI 0.72 to 14.57; 42 participants; one study; very low-quality evidence). Similarly, we are uncertain whether myomectomy reduces miscarriage rate for intramural fibroids (OR 1.33, 95% CI 0.26 to 6.78; 45 participants; one study; very low-quality evidence), submucous fibroids (OR 1.27, 95% CI 0.27 to 5.97; 52 participants; one study; very low-quality evidence), intramural/subserous fibroids (OR 0.80, 95% CI 0.10 to 6.54; 31 participants; one study; very low-quality evidence) or intramural/submucous fibroids (OR 2.00, 95% CI 0.32 to 12.33; 42 participants; one study; very low-quality evidence). This study did not report on live birth, preterm delivery, ongoing pregnancy or caesarean section rate.

Laparoscopic myomectomy versus myomectomy by laparotomy or mini-laparotomy

Two studies compared laparoscopic myomectomy to myomectomy at laparotomy or mini-laparotomy. We are uncertain whether laparoscopic myomectomy compared to laparotomy or mini-laparotomy improves live birth rate (OR 0.80, 95% CI 0.42 to 1.50; 177 participants; two studies; I^2 = 0%; very low-quality evidence), preterm delivery rate (OR 0.70, 95% CI 0.11 to 4.29; participants = 177; two studies; I^2 = 0%, very low-quality evidence), clinical pregnancy rate (OR 0.96, 95% CI 0.52 to 1.78; 177 participants; two studies; I^2 = 0%, very low-quality evidence), ongoing pregnancy rate (OR 1.61, 95% CI 0.26 to 10.04; 115 participants; one study; very low-quality evidence), miscarriage rate (OR 1.25, 95% CI 0.40 to 3.89; participants = 177; two studies; I^2 = 0%, very low-quality evidence), or caesarean section rate (OR 0.69, 95% CI 0.34 to 1.39; participants = 177; two studies; I^2 = 21%, very low-quality evidence).

Monopolar resectoscope versus bipolar resectoscope

One study evaluated the use of two electrosurgical systems during hysteroscopic myomectomy. We are uncertain whether bipolar resectoscope use compared to monopolar resectoscope use improves live birth/ongoing pregnancy rate (OR 0.86, 95% CI 0.30 to 2.50; 68 participants; one study, very low-quality evidence), clinical pregnancy rate (OR 0.88, 95% CI 0.33 to 2.36; 68 participants; one study; very low-quality evidence), or miscarriage rate (OR 1.00, 95% CI 0.19 to 5.34; participants = 68; one study; very low-quality evidence). This study did not report on preterm delivery or caesarean section rate.

Authors' conclusions

There is limited evidence to determine the role of myomectomy for infertility in women with fibroids as only one trial compared myomectomy with no myomectomy. If the decision is made to have a myomectomy, the current evidence does not indicate a superior method (laparoscopy, laparotomy or different electrosurgical systems) to improve rates of live birth, preterm delivery, clinical pregnancy, ongoing pregnancy, miscarriage, or caesarean section. Furthermore, the existing evidence needs to be viewed with caution due to the small number of events, minimal number of studies and very low-quality evidence.

PLAIN LANGUAGE SUMMARY

Does surgical removal of fibroids improve fertility outcomes?

Review question

Cochrane authors reviewed the evidence about the effect on fertility with the surgical removal of fibroids in infertile women.

Background

Fibroids are the most common benign tumours of the female genital tract and commonly affect women of reproductive age. Fibroids occur in different parts of the womb and can vary in size and shape. Fibroids can lead to a variety of symptoms including heavy periods, pain, difficulty to conceive, or problems with pregnancy such as miscarriage and premature labour. In women wishing to preserve their fertility, it is possible to remove the fibroid while preserving the womb, an operation known as myomectomy. This procedure can be performed by laparotomy (open abdominal surgery), laparoscopic surgery (a key-hole through the abdomen) or hysteroscopic surgery (a key-hole through the neck of the womb) depending on the site and size of the fibroid. This review aimed to answer two questions. Firstly, whether myomectomy led to an improvement in fertility; and secondly, if the procedure is beneficial, what is the ideal surgical approach?

Study characteristics

This review included four studies with 442 participants. One study compared myomectomy to no treatment. The remaining three studies compared different surgical methods of performing a myomectomy. The evidence is current to February 2019.

Key results

One study examined the effect of myomectomy compared to no treatment. Results found insufficient evidence to determine a difference between treatment options for clinical pregnancy rate or miscarriage rate. This study did not report on live birth, preterm delivery, ongoing pregnancy or caesarean section rate. Regarding the best surgical approach, three studies were identified. Two studies compared

myomectomy by mini-laparotomy or laparotomy to laparoscopic myomectomy and found insufficient evidence to determine a difference for live birth, preterm delivery, clinical pregnancy, miscarriage, caesarean section and ongoing pregnancy rate. The third study compared use of different surgical equipment during hysteroscopic myomectomy and found insufficient evidence to determine a difference for live birth/ongoing pregnancy rate, clinical pregnancy rate and miscarriage rate. This study did not report on caesarean section or preterm delivery rate. It is clear that more studies are needed before a consensus can be reached on the role of myomectomy for infertility.

Quality of evidence

The evidence was very low quality. There are some concerns regarding how the data were analysed and therefore the evidence cannot be considered to be conclusive until further studies are available.

Summary of findings for the main comparison. Myomectomy compared to no treatment for fibroids for infertility

Myomectomy compared to no treatment for fibroids for infertility

Patient or population: fibroids for infertility
Setting: tertiary care
Intervention: myomectomy
Comparison: no treatment

Outcomes	Anticipated absolute effects* (95% CI)			Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Without Myomectomy	With Myomectomy	Difference				
Live birth rate	No study data available						
Preterm delivery rate	No study data available						
Clinical pregnancy rate - Intramural	40.9%	56.5% (28.3 to 81)	15.6% more (12.6 fewer to 40 more)	OR 1.88 (0.57 to 6.14)	45 (1 RCT)	⊕⊖⊖⊖ VERY LOW [a, b]	
Clinical pregnancy rate - Submucous	27.3%	43.3% (18.9 to 71.4)	16.1% more (8.4 fewer to 44.1 more)	OR 2.04 (0.62 to 6.66)	52 (1 RCT)	⊕⊖⊖⊖ VERY LOW [a, b]	
Clinical pregnancy rate - Intramural/Subserous	21.4%	35.3% (9.8 to 73.3)	13.9% more (11.6 fewer to 51.9 more)	OR 2.00 (0.40 to 10.09)	31 (1 RCT)	⊕⊖⊖⊖ VERY LOW [a, b]	
Clinical pregnancy rate - Intramural/Submucous	15.0%	36.4% (11.3 to 72)	21.4% more (3.7 fewer to 57 more)	OR 3.24 (0.72 to 14.57)	42 (1 RCT)	⊕⊖⊖⊖ VERY LOW [a, b]	
Ongoing pregnancy rate	No study data available						
Miscarriage Rate - Intramural	13.6%	17.4% (3.9 to 51.7)	3.8% fewer (9.7 fewer to 38.1 more)	OR 1.33 (0.26 to 6.78)	45 (1 RCT)	⊕⊖⊖⊖	

						VERY LOW [a, b]
Miscarriage Rate - Submucous	13.6%	16.7% (4.1 to 48.5)	3.1% fewer (9.5 fewer to 34.9 more)	OR 1.27 (0.27 to 5.97)	52 (1 RCT)	⊕⊖⊖⊖ VERY LOW [a, b]
Miscarriage Rate - Intramural/Subserous	14.3%	11.8% (1.6 to 52.2)	2.5% fewer (12.6 fewer to 37.9 more)	OR 0.80 (0.10 to 6.54)	31 (1 RCT)	⊕⊖⊖⊖ VERY LOW [a, b]
Miscarriage Rate - Intramural/Submucous	10.0%	18.2% (3.4 to 57.8)	8.2% fewer (6.6 fewer to 47.8 more)	OR 2.00 (0.32 to 12.33)	42 (1 RCT)	⊕⊖⊖⊖ VERY LOW [a, b]
Caesarean section rate	No study data available					

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). **CI:** Confidence interval; **OR:** Odds ratio; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a] Downgraded two levels for indirectness; population sampled limited (single fibroid of max. 4 cm diameter); outcomes assessed could have included late birth outcome
[b] Downgraded one level for imprecision; no sample size calculation, there is only one study and small number of events

Summary of findings 2. Laparoscopic myomectomy compared to myomectomy by laparotomy or mini-laparotomy for fibroids for infertility

Laparoscopic myomectomy compared to myomectomy by laparotomy or mini-laparotomy for fibroids for infertility

Patient or population:fibroids for infertility
Setting: tertiary care
Intervention: laparoscopic myomectomy
Comparison: myomectomy by laparotomy or mini-laparotomy

Outcomes	Anticipated absolute effects* (95% CI)			Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Without Laparoscopic	With Laparoscopic myomectomy	Difference				

	myomectomy					
Live birth rate	36.3%	31.4% (19.3 to 46)	5.0% fewer (17 fewer to 9.8 more)	OR 0.80 (0.42 to 1.50)	177 (2 RCTs)	⊕⊖⊖⊖ VERY LOW [a, b, c]
Preterm delivery rate	3.3%	2.3% (0.4 to 12.8)	1.0% fewer (2.9 fewer to 9.5 more)	OR 0.70 (0.11 to 4.29)	177 (2 RCTs)	⊕⊖⊖⊖ VERY LOW [a, b, c]
Clinical pregnancy rate	45.1%	44.0% (29.9 to 59.3)	1.0% fewer (15.2 fewer to 14.3 more)	OR 0.96 (0.52 to 1.78)	177 (2 RCTs)	⊕⊖⊖⊖ VERY LOW [a, b, c]
Ongoing pregnancy rate	3.4%	5.3% (0.9 to 26.1)	2.0% more (2.5 fewer to 22.7 more)	OR 1.61 (0.26 to 10.04)	115 (1 RCT)	⊕⊖⊖⊖ VERY LOW [a, b, c, d]
Miscarriage Rate	6.6%	8.1% (2.7 to 21.5)	1.5% more (3.8 fewer to 14.9 more)	OR 1.25 (0.40 to 3.89)	177 (2 RCTs)	⊕⊖⊖⊖ VERY LOW [a, b, c]
Caesarean section rate	27.5%	20.9% (11.4 to 34.5)	6.8% fewer (16.1 fewer to 7 more)	OR 0.69 (0.34 to 1.39)	177 (2 RCTs)	⊕⊖⊖⊖ VERY LOW [a, b, c, e]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). **CI:** Confidence interval; **OR:** Odds ratio; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a] Downgraded one level for imprecision; no sample size calculation and small number of events
[b] Downgraded one level for imprecision; odds ratios and confidence intervals show opposing results
[c] Downgraded one level for indirectness; participants with multiple (3 and over), cavity distorting or submucosal fibroids excluded
[d] Downgraded one level for imprecision; only one study
[e] Downgraded one level for inconsistency; significant heterogeneity

Summary of findings 3. Monopolar resectoscope compared to bipolar resectoscope for hysteroscopic myomectomy for infertility

Monopolar resectoscope compared to bipolar resectoscope for hysteroscopic myomectomy for infertility

Patient or population: hysteroscopic myomectomy for infertility
Setting: tertiary care
Intervention: bipolar resectoscope use
Comparison: monopolar resectoscope use

Outcomes	Anticipated absolute effects* (95% CI)			Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Without Bipolar resectoscope use	With Bipolar resectoscope use	Difference				
Live birth rate/ ongoing pregnancy rate[a]	26.4%	29.4% (9.7 to 47.4)	3.5% more (16.7 fewer to 20.9 more)	OR 0.86 (0.30 to 2.50)	68 (1 RCT)	⊕⊖⊖⊖ VERY LOW [b, c]	
Preterm delivery rate	No study data available						
Clinical pregnancy rate	33.3%	38.2% (14.5 to 57)	3.3% more (20.8 fewer to 21.7 more)	OR 0.88 (0.33 to 2.36)	68 (1 RCT)	⊕⊖⊖⊖ VERY LOW [b, c]	
Miscarriage rate	8.8%	8.8% (1.8 to 34.1)	0% fewer (7 fewer to 25.2 more)	OR 1.00 (0.19 to 5.34)	68 (1 RCT)	⊕⊖⊖⊖ VERY LOW [b, c]	
Caesarean section rate	No study data available						

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). **CI:** Confidence interval; **OR:** Odds ratio; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a] Authors defined live birth rate/ongoing pregnancy rate > 30 weeks as a 'successful pregnancy outcome'
[b] Downgraded one level for imprecision; sample size calculated but not adhered to, only one study included and small number of events

[c] Downgraded two levels for indirectness; successful pregnancy outcome which included ongoing pregnancy rate and live birth rate; outcomes intended to be primarily fertility related, however the data presented are primarily surgical outcomes.

BACKGROUND

Description of the condition

Fibroids (also known as leiomyomas) are the most common benign tumours of the female genital tract and occur in about 20% to 50% of women (Yoshino 2010). They have been linked to many gynaecological problems including heavy menstrual bleeding and infertility. Fibroids are estimated to be the sole cause of infertility in less than 3% of cases (Farquhar 2009) and the mechanisms by which they can affect fertility vary depending on the type of fibroid. These mechanisms include causing possible anatomical changes affecting the cervix, uterus, tubes and ovaries, or causing a local endometrial inflammatory reaction leading to impaired endometrial receptivity, sperm transport or myometrial contractility (Inagaki 2003; Kroon 2011; Yoshino 2010; Yoshino 2012).

The evidence regarding the effect of fibroids on fertility depends mainly on the type of fibroid (submucous (SM), intramural (IM) or subserous (SS)), and this has been extensively reviewed in several studies (Somigliana 2007; Klatsky 2008; Pritts 2009; Sunkara 2010; Metwally 2011). Current evidence suggests the presence of an SM fibroid is detrimental for fertility, while SS fibroids seem to have little effect. The evidence regarding IM fibroids is less conclusive and there is no clear consensus regarding the effect of these fibroids on fertility outcomes.

Description of the intervention

Myomectomy is the procedure by which fibroids are removed whilst conserving the uterus. This procedure has been reported as far back as 1845, where the removal of an SS fibroid was described in the *American Journal of Medical Sciences* for a woman thought to have an ovarian cyst. The procedure was successful despite being performed in the pre-anaesthetic era through a midline incision. It was not until the early 20th century that myomectomy by laparotomy gained popularity, largely due to the haemostatic and surgical techniques developed by Victor Bonney (Chamberlain 2003). In the late 1970s, laparoscopic myomectomy was first described for SS fibroids, which extended to IM fibroids by the early 1990s (Dubuisso 2000). Since 2015, the routine use of laparoscopic myomectomy has fallen, following case reports of iatrogenic spreading of non-benign leiomyomas within the peritoneum during morcellation (permitting fibroid extraction from the abdomen through small incisions)(Hall 2015). Consequently, alternative techniques are favoured.

SM fibroids are currently predominantly managed using hysteroscopic resection techniques. Hysteroscopic myomectomy was pioneered largely as a consequence of development of the urological resectoscope. By the mid 1980s, instrument modifications led to the development of the gynaecological resectoscope with a 0° optical lens, a continuous flow irrigation system using 1.5% glycine and monopolar energy (Hallez 1995). Today, hysteroscopic myomectomy can also be performed by a bipolar resectoscope. Fundamentally, there are several important differences in electrosurgical systems. Use of a bipolar resectoscope allows the use of an electrolytic uterine distension medium such as normal saline (Sardo 2008; Metwally 2015). This medium, as opposed to the non-conducting distension medium used in monopolar procedures, can be used without the risk of adverse effects such as fluid overload, hyponatraemia and cerebral oedema (Emanuel 1997). Secondly, with the closed circuit seen in a bipolar electrosurgical system, the risk of spread of thermal energy is minimised, allowing a more precise tissue effect being exerted (Litta 2014b).

How the intervention might work

For some types of fibroids, such as SM fibroids where a clear negative effect on fertility has been demonstrated, myomectomy may improve fertility by restoring the normal anatomy of the uterus. With other types of fibroids, such as IM fibroids, the effect on fertility and therefore the effect of intervention on fertility remains less clear. It is possible that myomectomy may reverse some of the other associated abnormalities, such as the local endometrial inflammatory reaction, impaired gamete interaction and abnormal myometrial contractility, which could lead to improvement in implantation.

Why it is important to do this review

A societal shift in reproductive behaviour has meant women are more frequently delaying pregnancy until later in reproductive years. In 2017, 55% of mothers were aged 30 years and over, compared to 43% in 1997 (Office for National Statistics 2019). The delayed timing of pregnancy coincides with the peak incidence and diagnosis of fibroids. It is therefore predicted that by 2050, the number of myomectomies performed will increase by 31% (Wechter 2011). The majority of evidence reports an improvement in pregnancy rates (ranging from 10% to 77%) after myomectomy. This evidence is derived from case series rather than randomised controlled trials (Farquhar 2009). In addition, myomectomy carries inherent risks that may be detrimental to fertility. Myomectomy can reduce chances of conception due to peritoneal and intrauterine adhesions. Furthermore, the procedure prolongs time to conception due to surgical recovery. Additionally, laparoscopic myomectomy and myomectomy by laparotomy or mini-laparotomy increases the risk of scar rupture in a future pregnancy. It is therefore essential to determine the relationship between myomectomy and reproductive outcomes based on high-quality randomised controlled studies. Furthermore, considering the heterogenous nature of fibroids, it is essential that clinicians have clear guidance on when intervention is appropriate based on type of fibroid (SM, IM, SS).

OBJECTIVES

To examine the effect of myomectomy on fertility outcomes and to compare different surgical approaches.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials (RCTs) examining the effect of myomectomy compared to no treatment or a different surgical method were eligible for inclusion. Cross-over trials were not applicable in this context. Studies examining the effect of fibroid embolisation were not included as these are included in a separate review (Gupta 2014).

Types of participants

Women with uterine fibroids seeking infertility treatment, with or without symptoms.

Types of interventions

Surgical removal of fibroids by myomectomy at laparotomy, laparoscopy or hysteroscopy compared to no intervention or a different surgical method.

Types of outcome measures

Primary outcomes

1. Live birth rate (LBR), defined as the number of live births per woman

2. Preterm delivery rate (PDR) per woman

Secondary outcomes

3. Clinical pregnancy rate (CPR) per woman

4. Ongoing pregnancy rate (OPR) per woman, defined as a pregnancy progressing beyond 12 weeks of gestation

5. Miscarriage rate (MR) per woman

6. Caesarean section rate (CSR) per woman

Search methods for identification of studies

Electronic searches

The following databases were searched

1. The Cochrane Gynaecology and Fertility Group (CGF) Specialised Register of Controlled Trials; PROCITE platform, searched 26 February 2019 (Appendix 1)
2. CENTRAL via The Cochrane Register of Studies Online (CRSO); web platform, searched 26 February 2019 (Appendix 2)
3. MEDLINE; Ovid platform, searched from 1946 to 26 February 2019 (Appendix 3)
4. Embase Ovid platform, searched from 1980 to 26 February 2019 (Appendix 4)
5. PsycINFO Ovid platform, searched from 1806 to 26 February 2019 (Appendix 5)
6. CINAHL; (Cumulative Index to Nursing and Allied Health Literature), EBSCO platform, searched from 1961 to 26 February 2019 (Appendix 6)

The MEDLINE search was combined with the Cochrane highly sensitive search strategy for identifying randomised trials, which appears in the *Cochrane Handbook of Systematic Reviews of Interventions* Version 5.1.0 (Chapter 6, 6.4.11) (Higgins 2011).
The Embase, PsychINFO and CINAHL search were combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (https://www.sign.ac.uk/search-filters.html). There was no language restriction in these searches.

Other electronic sources of trials included (January 2012 to April 2019).

1. Epistemonikos database (https://www.epistemonikos.org/en)
2. World Health Organization International Clinical Trials Registry Platform search portal (http://www.who.int/trialsearch/Default.aspx)
3. LILACS database, which provides a source of trials from the Portuguese and Spanish speaking world (http://regional.bvsalud.org/php/index.php?lang=en)
4. PubMed and Google Scholar (for recent trials not yet indexed in major databases)
5. Grey literature (http://www.opengrey.eu/)

The following journals were also searched electronically (January 2012 to April 2019).

1. Fertility and Sterility
2. Human Reproduction
3. Obstetrics and Gynecology
4. American Journal of Obstetrics and Gynecology
5. British Journal of Obstetrics and Gynaecology
6. European Journal of Obstetrics, Gynecology, and Reproductive Biology
7. Gynaecological Endoscopy
8. Surgical Endoscopy

Searching other resources

We handsearched reference lists of articles retrieved by the search and contacted experts in the field to obtain additional data. Previously excluded studies in this review were reassessed for eligibility. We also handsearched relevant journals and conference abstracts that are not covered in the CGF register, in liaison with the Information Specialist.

Data collection and analysis

Selection of studies

Titles and abstracts were screened independently by two review authors (GR and MM) to exclude studies that were clearly irrelevant. Full texts of potentially eligible studies were then retrieved and examined independently by GR and MM for compliance with the predefined inclusion criteria. We corresponded with study investigators as required to clarify study eligibility. Any disagreements regarding eligibility were resolved at a subsequent meeting. The selection process was documented with a PRISMA flow chart.

Data extraction and management

Two review authors (GR and MM) independently extracted data using a data extraction form designed and pilot-tested by the review authors. Study characteristics and outcome data were extracted (see data extraction table for details, Appendix 7). When studies had multiple publications, the review authors collated all reports of the same study under a single study ID with multiple references. Where data were missing or unclear, we corresponded with study investigators for further data on methods and/or results, as required.

Assessment of risk of bias in included studies

Two review authors (GR and MM) independently assessed included studies for risk of bias using the Cochrane 'Risk of bias' assessment tool (*Cochrane Handbook of Systematic Reviews of Interventions*

Version 5.1.0) (Higgins 2011). Seven domains were assessed: selection bias (random sequence generation), selection bias (allocation concealment), attrition bias (incomplete outcome data), reporting bias (selective reporting), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessors), and other biases (other problems that could put a trial at high risk of bias). Judgements were assigned as recommended in the Cochrane Handbook Section 8.5 (Higgins 2011). Any disagreements were resolved by consensus. We described all the judgements fully and presented the conclusions in the 'Risk of bias' tables.

Measures of treatment effect

We performed statistical analysis in accordance with the guidelines developed by the Cochrane Gynaecology and Fertility group. Dichotomous data were retrieved and analysed using the Mantel-Haenszel odds ratios (ORs) with 95% confidence intervals (CIs).

Unit of analysis issues

The primary analysis is presented as per woman randomised. If relevant, rate per clinical pregnancy was used as the denominator for a secondary analysis of preterm delivery rate, miscarriage rate, and caesarean section rate as this helps to give a full picture.

Dealing with missing data

In the situation that data were missing, we contacted trial authors. In situations where attempts for correspondence were unsuccessful, missing data were analysed using intention-to-treat basis. Individual values were imputed when missing data included primary outcome live birth rate only: live birth rate were assumed not to have occurred in participants without a reported outcome. We planned that any imputation undertaken would be subjected to sensitivity analysis. For other outcomes, we analysed only the available data.

Assessment of heterogeneity

We considered whether the clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary. Heterogeneity was assessed using the I^2 statistic according to the guidelines set out in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). An I^2 measurement greater than 50% indicated substantial heterogeneity.

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, we aimed to minimise their potential impact by ensuring a comprehensive search for eligible studies and by being alert for duplication of data. If there were 10 or more studies in an analysis, we planned to use a funnel plot to explore the possibility of small-study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies).

Data synthesis

When studies were sufficiently similar, dichotomous data for primary and secondary outcomes were combined using a fixed-effect model. An increase in the odds of a particular outcome, which may be beneficial (for example live birth) or detrimental (for example preterm delivery), is displayed graphically in the meta-analysis to the right of the centre-line and a decrease in the odds of an outcome to the left of the centre line.

Subgroup analysis and investigation of heterogeneity

Where possible, outcomes were examined in subgroups depending on the type of fibroid (SM, IM and SS).

Sensitivity analysis

For comparisons where primary outcomes were deemed as a high risk of bias, we planned to perform a sensitivity analysis.

Overall quality of the body of evidence: 'Summary of findings' tables

A 'Summary of findings' table was generated using GRADEpro and Cochrane methods (Higgins 2011; GRADEpro GDT 2015). This table evaluated the overall quality of the body of evidence for the main review outcomes (live birth rate, preterm delivery rate, clinical pregnancy rate, ongoing pregnancy rate, caesarean section rate and miscarriage rate) for the main review comparison (myomectomy versus no treatment). Additional 'Summary of findings' tables were prepared for the main review outcomes of other important comparisons (myomectomy performed by laparotomy or mini-laparotomy versus laparoscopic myomectomy, and monopolar versus bipolar resectoscope use in hysteroscopic myomectomy). The quality of the evidence was assessed using the GRADE criteria: risk of bias, consistency, precision, directness and publication bias. Judgements regarding the evidence quality (high, moderate, low or very low) have been justified, documented, and incorporated into reporting of results for each outcome.

RESULTS

Description of studies

See tables for Characteristics of included studies, Characteristics of excluded studies and Characteristics of ongoing studies

Results of the search

An updated search revealed 1570 articles. Fourteen studies were potentially eligible and were retrieved in full text. Eleven did not fulfil the inclusion criteria and were therefore excluded (Spies 2010; Chatterjee 2012; Kim 2013; Wang 2013; Litta 2014; Seyam 2015; Kramer 2016 Wang 2016; Saleh 2018 Sato 2018; Wen 2018). Two studies were not included as they were ongoing trials (NCT03143114; NCT03796130). One new study was included (Roy 2017), which was added to the three studies included in the previous version of the review (Seracchioli 2000; Casini 2006; Palomba 2007). Study selection is documented in a Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart shown in Figure 1.

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart.

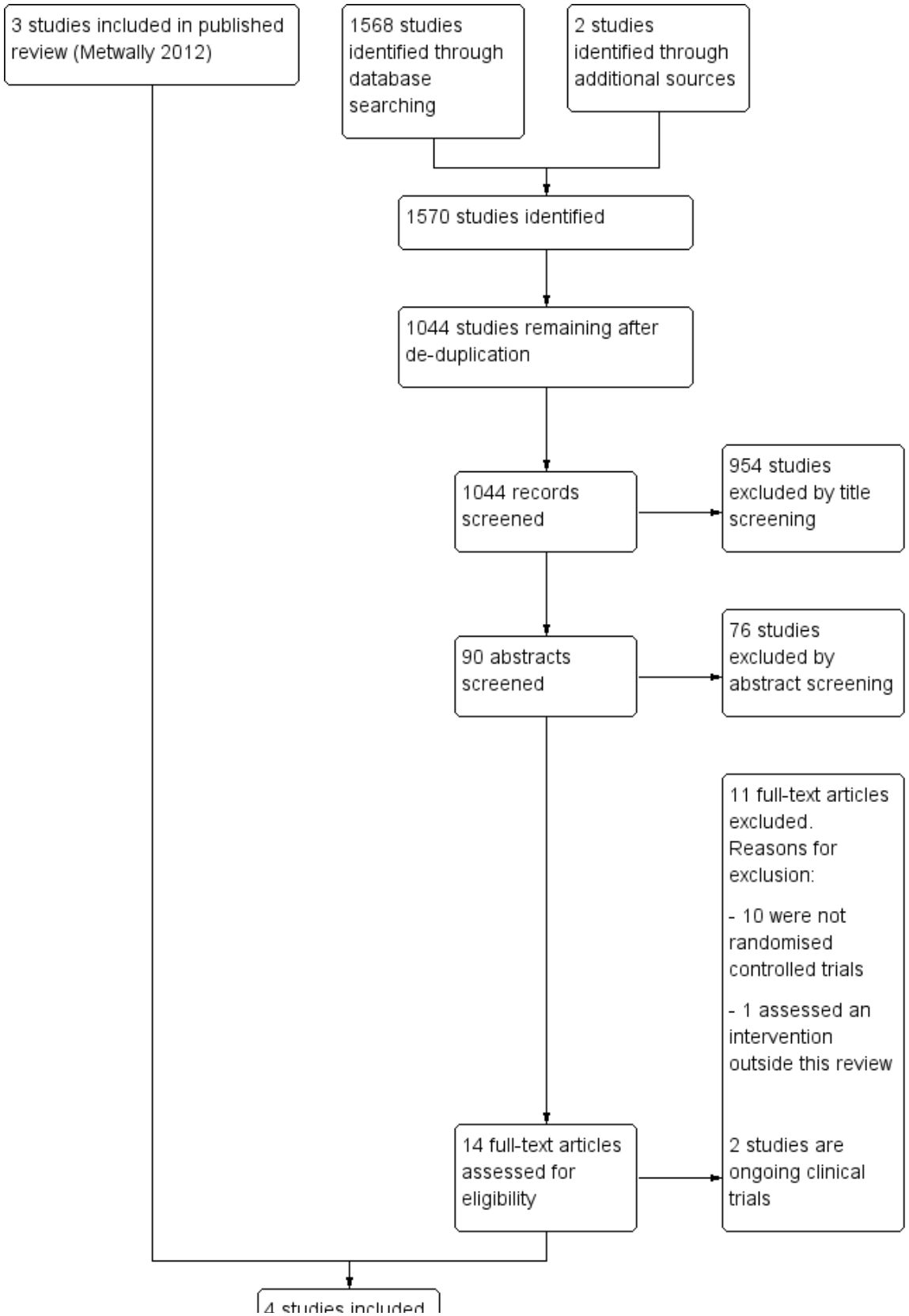
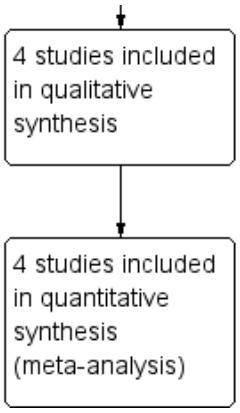


Figure 1. (Continued)



Included studies

Study design and setting

Four parallel-design randomised controlled trials (RCTs) were included in the review. Three were single-centre studies (Seracchioli 2000; Casini 2006; Roy 2017), and one was a multi-centre study (Palomba 2007) conducted at three university hospitals. Three studies were conducted in Italy and one was conducted in India.

Participants

One study (Casini 2006) compared myomectomy (hysteroscopic myomectomy or myomectomy by laparotomy) to no intervention. It included 92 women in the intervention group and 89 patients in the control group. Two studies compared myomectomy at laparotomy or mini-laparotomy to laparoscopic myomectomy (Seracchioli 2000; Palomba 2007). These two studies included 86 women in the laparoscopic groups and 91 in the laparotomy/mini-laparotomy groups. The fourth study (Roy 2017) included women undergoing hysteroscopic myomectomy by either monopolar or bipolar resectoscope and included 34 women for each group.

Three studies included only women suffering from infertility (Seracchioli 2000; Casini 2006; Roy 2017). The fourth study (Palomba 2007), included women with symptomatic fibroids and women with unexplained infertility. Only the women with unexplained infertility were included within the analysis.

Interventions

1. 1/4 studies compared hysteroscopic myomectomy or myomectomy by laparotomy to no treatment (Casini 2006)
2. 2/4 studies compared myomectomy at laparotomy or mini-laparotomy to laparoscopic myomectomy (Seracchioli 2000; Palomba 2007)
3. 1/4 studies compared monopolar resectoscope use to bipolar resectoscope use in hysteroscopic myomectomy (Roy 2017)

Outcomes

1. 3/4 studies reported live birth (Seracchioli 2000; Palomba 2007; Roy 2017)
2. 2/4 reported preterm delivery (Seracchioli 2000; Palomba 2007)
3. 4/4 studies reported on clinical pregnancy
4. 2/4 reported ongoing pregnancy (Seracchioli 2000; Roy 2017)
5. 4/4 reported miscarriage
6. 2/4 reported caesarean section (Seracchioli 2000; Palomba 2007)

Characteristics of fibroids

Regarding the type of fibroid, only one study subcategorised outcomes by the type of fibroid (Casini 2006). Outcomes were reported separately for intramural; (IM), subserous (SS) and submucous (SM) fibroids as well as combinations of different types. Different methods of surgery were used to perform myomectomy (by either laparotomy or hysteroscopy). However, data were not provided for these techniques separately. The other studies did not specify outcomes by type of fibroid (IM or SS), although authors stated SM fibroids were excluded (Seracchioli 2000; Palomba 2007). The study completed by Roy 2017 evaluated SM fibroids only as the intervention under evaluation in this study permits resection of this type of fibroid only.

Regarding the number and size of fibroid, in the study by Casini 2006, only single fibroids with a maximum diameter of 4 cm were included. Similarly, Roy 2017 included participants with fibroids under 3 cm in diameter, but allowed a maximum of two fibroids. Size and number were more variable in the other two included studies. In the study by Palomba 2007, participants had less than three fibroids, with a diameter between 3 cm and 10 cm. In the study by Seracchioli 2000, a maximum of three fibroids were included with fibroids being 5 cm or more.

Further details of included studies can be found in the table Characteristics of included studies.

Excluded studies

In this version of the review 11 studies were excluded for the following reasons:

1. 10/11 were not RCTs (Spies 2010; Chatterjee 2012; Kim 2013; Wang 2013; Litta 2014; Seyam 2015; Wang 2016; Saleh 2018; Sato 2018; Wen 2018);
2. 1/11 assessed an intervention outside of our review (Kramer 2016).

Characteristics of all excluded studies can be found in the table Characteristics of excluded studies.

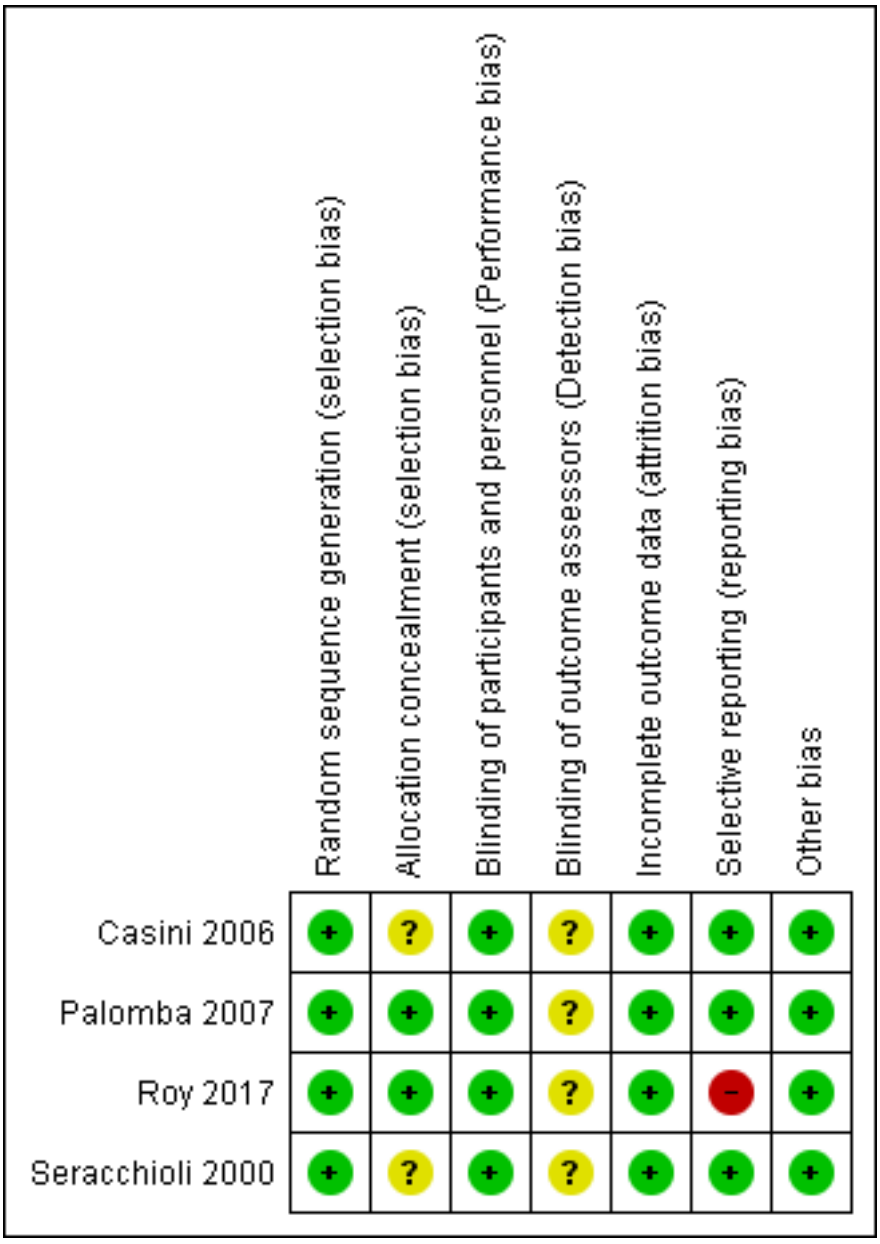
Ongoing studies

There are two ongoing clinical trials (NCT03143114; NCT03796130).

Risk of bias in included studies

'Risk of bias' assessment focused on seven domains: generation of allocation sequence, concealment of allocation sequence, blinding of participants and personnel, blinding of outcome assessor, incomplete outcome data, selective outcome reporting and other bias (e.g. publication bias). Details of findings can be found in the relevant 'Risk of bias' summary figure (Figure 2) and the table Characteristics of included studies.

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation

All four studies were at low risk of selection bias related to sequence generation as they used computer randomisation or a random numbers table.

Allocation concealment

Two studies were at low risk of selection bias related to allocation concealment as the random allocation sequence was concealed in a closed and dark-coloured envelope until immediately prior to surgery (Palomba 2007, Roy 2017). The other two studies did not describe the method used and were therefore deemed to have an unclear risk of this bias.

Blinding

Blinding of participants and personnel (performance bias)

As expected, blinding of participants and personnel was not performed in surgical studies. Therefore, the absence of blinding was not considered a source of bias.

Blinding of outcome assessors (detection bias)

It was unclear in all four studies if outcome assessors were blinded to which intervention a participant received.

Incomplete outcome data

All studies analysed all women randomised and we judged them to be at low risk of bias.

Selective reporting

Three of four studies reported on all prespecified outcomes and therefore all three studies were judged to be at low risk of bias (Seracchioli 2000; Casini 2006; Palomba 2007). The fourth study only reported on four of five pre-specified reproductive outcomes and was therefore deemed high risk of reporting bias (Roy 2017). Furthermore, this study combined outcomes and reported them as a single entity. 'Successful pregnancy outcome' was reported as a combination of live birth rate and ongoing pregnancy rate (> 30 weeks), without explanation. Finally, whilst Casini 2006 reported on all pre-specified outcomes, it could be considered to be at a high risk of reporting bias as live birth rate was not reported despite the trial lasting seven years.

Other potential sources of bias

We found no other potential sources of bias in any of the included studies.

Effects of interventions

See: **Summary of findings for the main comparison** Myomectomy compared to no treatment for fibroids for infertility; **Summary of findings 2** Laparoscopic myomectomy compared to myomectomy by laparotomy or mini-laparotomy for fibroids for infertility; **Summary of findings 3** Monopolar resectoscope compared to bipolar resectoscope for hysteroscopic myomectomy for infertility

1. Comparison of myomectomy versus no intervention.

Results were reported from one study (Casini 2006).

Primary outcomes

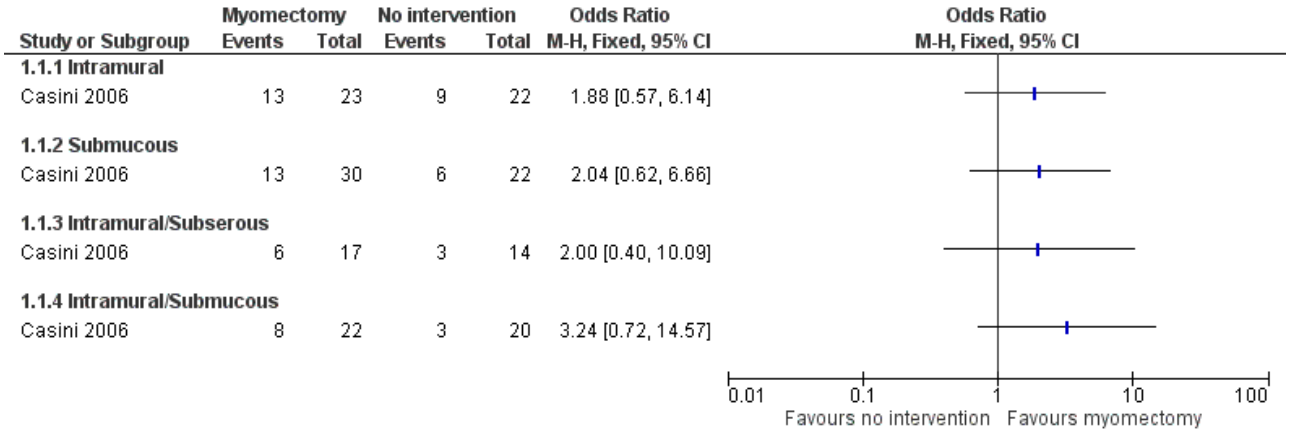
1.1 Live birth rate: not reported.

1.2 Preterm delivery rate: not reported.

Secondary outcomes

1.3 Clinical pregnancy rate: we are uncertain whether myomectomy improves clinical pregnancy rate for intramural (IM) fibroids (OR 1.88, 95% CI 0.57 to 6.14, participants = 45; studies = 1; very low-quality evidence), submucous (SM) fibroids (OR 2.04, 95% CI 0.62 to 6.66; participants = 52; studies = 1; very low-quality evidence), combined intramural/subserous (IM/SS) fibroids (OR 2.00, 95% CI 0.40 to 10.09; participants = 31; studies = 1; very low-quality evidence) and combined intramural/submucous (IM/SM) fibroids (OR 3.24, 95% CI 0.72 to 14.57; participants = 42; studies = 1; very low-quality evidence) (Analysis 1.1: see Figure 3).

Figure 3. Forest plot of comparison 1: Myomectomy versus no intervention, Outcome 1.3: Clinical pregnancy rate.



For IM fibroids, chance of pregnancy without myomectomy was assumed to be 41%, compared to between 28% and 81% with myomectomy. For SM fibroids, chance of pregnancy without myomectomy was assumed to be 27%, compared to between 19% and 71% with myomectomy. For IM/SS fibroids, chance of pregnancy without myomectomy was assumed to be 21%, compared to between 10% and 73% with myomectomy. For IM/SM fibroids, chance of pregnancy without myomectomy was assumed to be 15%, compared to between 11% and 72% with myomectomy.

1.4 Ongoing pregnancy rate: not reported.

1.5 Miscarriage rate: we are uncertain whether myomectomy reduces miscarriage rate for IM fibroids (OR 1.33, 95% CI 0.26 to 6.78; 45 participants; one study; very low-quality evidence), SM fibroids (OR 1.27, 95% CI 0.27 to 5.97; 52 participants; one study; very low-quality evidence), combined IM/SS fibroids (OR 0.80, 95% CI 0.10 to 6.54; 31 participants; one study; very low-quality evidence) and combined IM/SM fibroids (OR 2.00, 95% CI 0.32 to 12.33; 42 participants; one study; very low-quality evidence).

For IM fibroids, chance of miscarriage without myomectomy was 14% compared to between 4% and 52% with myomectomy. For SM fibroids, chance of miscarriage without myomectomy was 14% compared to between 4% and 49% with myomectomy. For IM/SS fibroids, chance of miscarriage without myomectomy was 14% compared to between 2% and 52% with myomectomy. For IM/SM fibroids, chance of miscarriage without myomectomy was 10% compared to between 3% and 58% with myomectomy.

1.6 Caesarean section rate: not reported.

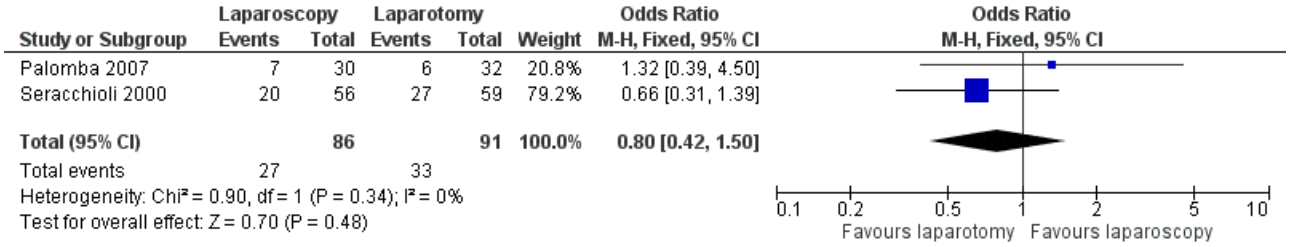
2. Comparison of myomectomy at laparotomy or mini-laparotomy versus laparoscopic myomectomy

Results were reported from two studies (Seracchioli 2000; Palomba 2007).

Primary outcomes

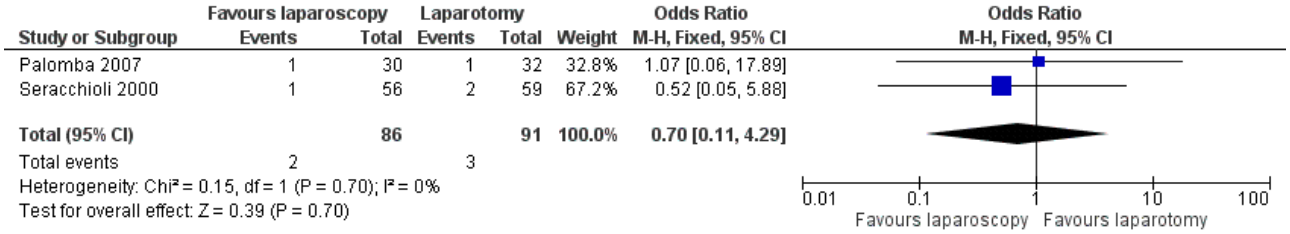
2.1 Live birth rate: we are uncertain whether laparoscopic myomectomy improves live birth rate compared to myomectomy at laparotomy or mini-laparotomy (OR 0.80, 95% CI 0.42 to 1.50; participants = 177; studies = 2; I^2 = 0%; very low-quality evidence). This evidence suggests that the birth rate in those receiving myomectomy by laparotomy or mini-laparotomy is assumed to be 36%, compared to between 19% and 46% for those receiving laparoscopic myomectomy. (Analysis 2.1: see Figure 4).

Figure 4. Forest plot of comparison 2: Laparoscopic myomectomy versus myomectomy at laparotomy or mini-laparotomy, Outcome 2.1: Live birth rate.



2.2 Preterm delivery rate: we are uncertain whether laparoscopic myomectomy reduces preterm delivery rate compared to myomectomy at laparotomy or mini-laparotomy (OR 0.70, 95% CI 0.11 to 4.29; participants = 177; studies = 2; I^2 = 0%; very low-quality evidence). This evidence suggests that the preterm delivery rate in those receiving myomectomy by laparotomy or mini-laparotomy is assumed to be 3%, compared to between 0% and 13% for those receiving laparoscopic myomectomy. (Analysis 2.2: see Figure 5).

Figure 5. Forest plot of comparison 2: Laparoscopic myomectomy versus myomectomy at laparotomy or mini-laparotomy, Outcome 2.2: Preterm delivery rate.



Secondary outcomes

2.3 Clinical pregnancy rate: we are uncertain whether laparoscopic myomectomy improves clinical pregnancy rate compared to myomectomy at laparotomy or mini-laparotomy (OR 0.96, 95% CI 0.52 to 1.78; participants = 177; studies = 2; I^2 = 0%; very low-quality evidence) (Analysis 2.3). This evidence suggests that the clinical pregnancy rate in those receiving myomectomy by laparotomy or mini-laparotomy is 45% compared to between 30% and 59% receiving laparoscopic myomectomy.

2.4 Ongoing pregnancy rate: we are uncertain whether laparoscopic myomectomy improves ongoing pregnancy rate compared to myomectomy at laparotomy or mini-laparotomy (OR 1.16, 95% CI 0.26 to 10.04, participants = 115; studies = 1; very low-quality evidence) (Analysis 2.4). This evidence suggests that the chances of an ongoing pregnancy in those receiving myomectomy by laparotomy or mini-laparotomy is assumed to be 3%, the chance with laparoscopic myomectomy would be between 1% and 26%.

2.5 Miscarriage rate: we are uncertain whether laparoscopic myomectomy reduces miscarriage rate compared to myomectomy at laparotomy or mini-laparotomy (OR 1.25, 95% CI 0.40 to 3.89; participants = 177; studies = 2; I^2 = 0%; very low-quality evidence) (Analysis 2.5). This evidence suggests that the chances of a miscarriage in those receiving myomectomy by laparotomy or mini-laparotomy is assumed to be 7%, the chance with laparoscopic myomectomy would be between 3% and 22%.

2.6 Caesarean section rate: we are uncertain whether laparoscopic myomectomy improves caesarean section rate compared to

myomectomy at laparotomy or mini-laparotomy (OR 0.69, 95% CI 0.34 to 1.39; participants = 177; studies = 2; I^2 = 21%; very low-quality evidence) (Analysis 2.6). This evidence suggests that the chances of having a caesarean section in those receiving myomectomy by laparotomy or mini-laparotomy is assumed to be 28%, compared to between 11% and 35% in those receiving laparoscopic myomectomy.

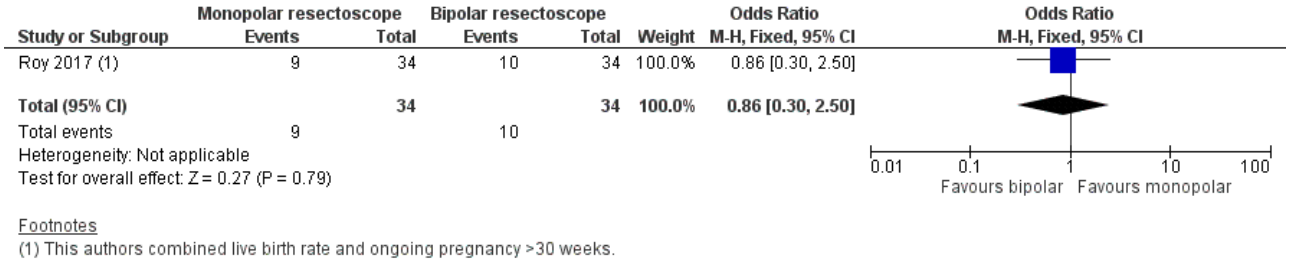
3. Comparison of monopolar versus bipolar resectoscope use in hysteroscopic myomectomy

Results were reported from one study (Roy 2017).

Primary outcomes

3.1 Live birth/ongoing pregnancy rate (defined by authors as a 'successful pregnancy outcome' > 30 weeks): we are uncertain whether bipolar resectoscope use improves live birth/ongoing pregnancy rate compared to monopolar resectoscope use in hysteroscopic myomectomy (OR 0.86, 95% CI 0.30 to 2.50, participants = 68; studies = 1; very low-quality evidence). Therefore meaning that in those receiving monopolar resectoscope use in hysteroscopic myomectomy, the birth rate was assumed to be 26.4%, compared to between 10% and 47% in those who had a myomectomy with a bipolar resectoscope. (Analysis 3.1: see Figure 6).

Figure 6. Forest plot of comparison 3: Monopolar versus bipolar resectoscope use in hysteroscopic myomectomy, Outcome 3.1 Live birth rate/Ongoing pregnancy rate.



3.2 Preterm delivery rate: not reported.

Secondary outcomes

3.3 Clinical pregnancy rate: we are uncertain whether bipolar resectoscope use improves clinical pregnancy rate compared to monopolar resectoscope use in hysteroscopic myomectomy (OR 0.88, 95% CI 0.33 to 2.36, participants = 68; studies = 1; very low-quality evidence) (Analysis 3.2). Therefore meaning that in those receiving a myomectomy using a monopolar resectoscope, clinical pregnancy rate was assumed to be 33.3%, compared to between 15% and 57% in those who had a myomectomy with a bipolar resectoscope.

3.4 Ongoing pregnancy rate: reported above with live birth rate.

3.5 Miscarriage rate: we are uncertain whether bipolar resectoscope use reduces miscarriage rate compared to monopolar resectoscope use in hysteroscopic myomectomy (OR 1.00, 95% CI 0.19 to 5.34; participants = 68; studies = 1; very low-quality evidence) (Analysis 3.3). Therefore meaning that in those receiving a myomectomy using a monopolar resectoscope, miscarriage rate was assumed to be 9%, compared to between 2% and 34% in those who had a myomectomy with a bipolar resectoscope.

3.6 Caesarean section rate: not reported.

Effects of subgroup analysis

Subgroup analysis permitted examination of effect of intervention on fibroids in different locations. Only one study reported on location of fibroids individually, which meant there were too few studies to perform the planned subgroup analysis.

Effects of sensitivity analysis

As no single comparison included a study with a primary outcome deemed as a high risk of bias, a sensitivity analysis was not performed. Furthermore, there were too few studies to conduct sensitivity analysis.

DISCUSSION

Summary of main results

This review included four randomised controlled studies (RCTs) (442 participants) that examined the effect of myomectomy on fertility outcomes. When examining this issue, two questions need to be answered. Firstly, whether myomectomy leads to an improvement in fertility outcomes; and secondly, if there is a beneficial effect what would be the ideal surgical approach?

The first question was addressed by only one randomised controlled trial (Casini 2006). This study appropriately examined reproductive outcomes separately for the different types of fibroids. We are uncertain of the effect myomectomy had on both clinical pregnancy and miscarriage rate compared to no treatment. Unfortunately this study did not report on either primary outcome (live birth rate or preterm delivery rate), despite the study lasting seven years. Furthermore, the study collectively reported on myomectomies performed either by laparotomy or hysteroscopy, meaning separate analysis of these two very different surgical approaches could not be performed.

The second question was addressed by three studies (Seracchioli 2000, Palomba 2007 and Roy 2017). Two studies compared myomectomy at laparotomy or mini-laparotomy to laparoscopic myomectomy (Palomba 2007; Seracchioli 2000). It is uncertain which surgical method is superior when comparing these approaches on fertility outcomes (live birth, preterm delivery,

clinical pregnancy, ongoing pregnancy, miscarriage and caesarean section rate). The third study (Roy 2017) compared monopolar versus bipolar resectoscope use in hysteroscopic myomectomy. It is uncertain which of the two approaches is superior regarding any of the reported fertility outcomes (live birth rate, clinical pregnancy rate and miscarriage rate).

Overall completeness and applicability of evidence

1. In determining the effect of myomectomy on fertility outcomes, fibroids are not a single entity but vary widely regarding site and size with different fertility effects being reported for intramural (IM), subserous (SS) and submucous (SM) fibroids. There is currently a consensus regarding the fertility effects for SS and SM fibroids, based on the findings of several case-controlled studies and meta-analyses. These studies suggest SM fibroids have been found to be associated with a negative impact on fertility while SS fibroids appeared to have little to no effect (Pritts 2009). Opinion regarding IM fibroids is more controversial. Some studies have suggested a negative effect on fertility (Pritts 2009; Sunkara 2010), while a more recent study has suggested that in fact the quality of evidence is too low to draw any conclusions (Metwally 2011). In the midst of such controversy, clinicians are left with a difficult task when deciding whether or not to surgically intervene, particularly when surgical intervention may itself pose a risk to fertility due to the risk of intrauterine and pelvic adhesions.

Unfortunately the current evidence does not settle this dilemma as only one study addressed reproductive outcomes separately for different types of fibroids (Casini 2006). The sample size was relatively small and therefore inadequate to draw a firm conclusion. Furthermore, the study was limited only to single fibroids of a maximum size of 4 cm. Finally, the study did not report on the live birth rate.

2. For type of surgical approach, evidence regarding the use of laparoscopy versus laparotomy was more comprehensive. While the use of the laparoscopic approach may offer advantages regarding postoperative recovery and morbidity, the current study was unable to identify any clear benefit for the laparoscopic approach regarding fertility outcomes. On the positive side, despite the small number of studies, both studies provided evidence regarding our primary outcome, live birth rate, as well as several secondary outcomes. Furthermore, information is provided regarding late pregnancy outcomes, that is preterm delivery and caesarean section rates. However, the difficulty with comparing the two abdominal approaches remains the fact that there is a large variation in surgical practice, for example level of skill, surgical technique and use of anti-adhesion agents, all of which may influence fertility outcomes. Therefore, until a larger number of studies is available, it would be difficult to draw a firm conclusion. Finally, SM fibroids are thought to have the strongest association with impaired fertility, with hysteroscopic myomectomy considered the most appropriate surgical approach. Despite the potential fertility implications, there is limited high-quality evidence available evaluating the intervention on reproductive outcomes. Only one RCT, attempts to make progress analysing this approach (Roy 2017). This study compared electrosurgical systems (monopolar to bipolar). Previously, both techniques have been shown to have successful pregnancy outcomes (Makris 2007; Litta 2014a). Results found that there was minimal difference between the two interventions on reproductive outcomes. Outside of our assessed outcomes, a greater difference was seen. Bipolar resectoscope use had better surgical outcomes, suggesting it would be a safer alternative.

Quality of the evidence

For the effect of myomectomy on fertility outcomes, the study by Casini 2006 had the advantage of clearly defining the type of fibroid, by only including single fibroids of 4 cm maximum diameter. Information regarding larger or multiple fibroids is however clearly lacking. Allocation concealment was not clear raising the possibility of selection bias. Furthermore, abdominal myomectomies and hysteroscopic myomectomies are two very different techniques dealing with different types of fibroids and with very different potential side effects that may have a negative impact on fertility (that is intrauterine versus peritubal adhesions). Therefore the inclusion of these two surgical approaches into one study group has the potential to introduce bias and further compromise the quality of the evidence.

For the surgical approach for myomectomy, three studies provided evidence. Only two studied myomectomy at laparotomy or mini-laparotomy compared to laparoscopic myomectomy (Seracchioli 2000; Palomba 2007), and therefore the evidence should be viewed with caution. The study by Seracchioli 2000 was not clear regarding allocation concealment. However a positive aspect of the analysis is that all outcomes were associated with no evidence of significant heterogeneity. The fourth study compared monopolar resectoscope use to bipolar resectoscope use in hysteroscopic myomectomy. As only one study provided evidence for this comparison, with only 60 participants, evidence must be viewed with caution. This study did perform a power calculation (Roy 2017). However, only 60 participants in total were recruited, despite the completed power calculation indicating needing a threshold of 100 participants per group for significant findings. Furthermore, this study had a high risk of reporting bias, as intended outcomes did not match reported outcomes.

Overall, the quality of evidence in this review was very low quality. Three studies included in the review did not perform a power calculation or explain the rationale behind their recruited sample size (Seracchioli 2000; Casini 2006; Palomba 2007). Furthermore, Palomba 2007 describes halting recruitment following an interim analysis due to quote "*too little or clinically irrelevant difference in outcomes to continue the study to obtain an adequate power*". As described by Kadam 2010, a sample size should always be performed prior to starting a trial and should not be altered during the study, meaning all three studies are likely to be underpowered and can be criticised.

Potential biases in the review process

Review authors MM and GR independently screened and identified relevant studies making it unlikely that any studies have been missed. Furthermore, a final search was performed at the completion of the review to ensure that no new studies had been published during preparation of the manuscript. However, despite all our efforts, there is still a possibility that studies in press may have been missed.

All review authors were in agreement regarding the inclusion or exclusion of any newly identified study, and therefore it is unlikely that a misjudgement has been made leading to the non-inclusion of any relevant study.

Agreements and disagreements with other studies or reviews

This review remains the only systematic review and meta-analysis to assess the role of myomectomy on fertility outcomes. SInce the review was last updated in 2012 (Metwally 2012), one new study has been included (Roy 2017) and primary outcomes have been reassessed. The previous version included two comparisons evaluating myomectomy compared to no treatment and different surgical approaches to myomectomy. The addition of a new study has permitted an expansion of the review to include a third comparison evaluating use of different electrosurgical systems in hysteroscopic myomectomy. Additionally, preterm delivery rate has been promoted to a primary outcome.The main findings however remain unchanged, where the insufficient number of studies prevents us from drawing a firm conclusion.

AUTHORS' CONCLUSIONS

Implications for practice

There remains limited evidence to determine the role of myomectomy for infertility in women with fibroids. If the decision is made to have a myomectomy, the current evidence does not indicate a superior method (laparoscopy, laparotomy or different electrosurgical systems) to improve rates of live birth, preterm delivery, clinical pregnancy, ongoing pregnancy, miscarriage, or caesarean section. Furthermore, the existing evidence needs to be viewed with caution due to the small number of events, minimal number of studies and very low-quality evidence.

Implications for research

There is an urgent need for high-quality randomised controlled studies to determine the role of myomectomy for fertility management, given that fibroids are not a single entity but a wide spectrum of tumours. Studies should therefore take into consideration the following points.

1. Priority should be given to studies comparing myomectomy to no intervention rather than comparing different types of surgical interventions. If a beneficial effect for surgery is demonstrated then the next step would be to focus on the type of surgical approach.
2. Studies should classify outcomes by the size and type of fibroid (intramural (IM), subserous (SS) and submucous (SM)) with clear definitions in the inclusion and exclusion criteria.
3. Inclusion of patients in future studies with only unexplained infertility would minimise the effect of other confounding factors such as differences in the cause of infertility.

ACKNOWLEDGEMENTS

This review is an updated version of the initial Cochrane review by Anthony N Griffiths, Arianna D'Angelo and Nazar N Amso (Griffiths 2006). We would like to acknowledge their valuable contribution.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Casini 2006

Methods	Randomised controlled trial
Participants	181 participants Treatment n = 92, No treatment = 89 Treatment (SM n = 30, IM n = 23, IM/SS n = 17, SM/IM n = 22) No treatment (SM n = 22, IM n = 22, SS n = 11, IM/SS n = 14, SM/IM n = 20) Participants woman with infertility and fibroids, with no other cause for infertility. Inclusion criteria: 1- age: < 35 years; 2- infertility for 1 year or more; 3- presence of one fibroid with maximum diameter of 40 mm. Exclusion criteria: 1- two or more fibroids with diameter more than 40 mm; 2- body weight more than 20% above normal weight; 3- use of medication containing oestrogens, progestins or androgens within 8 weeks prior to starting the study.
Interventions	Myomectomy at hysteroscopy or laparotomy or no intervention
Outcomes	1- Clinical pregnancy rate, defined as visualisation of an embryo with cardiac activity at 6–7 weeks of pregnancy. 2- Miscarriage rate, defined as clinical loss of an intrauterine pregnancy between 7th and 12th weeks of gestation.

Casini 2006 *(Continued)*

Notes	No power calculation Follow-up period: 12 months Funding: none stated Conflict of interest: none stated Study dates: 1998-2005 Trial registration number: unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation table
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (Performance bias) All outcomes	Low risk	Due to the nature of the intervention, personnel could not be blinded. Furthermore, participants could not be blinded as they either received surgery or did not. Therefore, performance bias was not considered a source of bias in this study.
Blinding of outcome assessors (Detection bias) All outcomes	Unclear risk	It remains unclear whether outcome assessors were blinded when analysis results (detection bias)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all patients who started the study
Selective reporting (reporting bias)	Low risk	All specified outcomes reported in the results section
Other bias	Low risk	No evidence of other bias

Palomba 2007

Methods	Randomised controlled trial
Participants	136 participants Participants had either symptomatic uterine leiomyomas (n = 74) or infertility (n = 62). Only unexplained fertility patients were analysed Laparoscopy n = 30 Laparotomy n = 32 Exclusion criteria: patient characteristics:1- major medical conditions and endocrine diseases, 2- basal FSH >10 IU/L, 3- psychiatric disorders, 4- current or past history of acute or chronic physical illness, 5- premenstrual syndrome, 6- current or past (within 6 months) use of hormonal medications, 7- medications influencing cognition, vigilance, or mood, 8- inability to complete the daily diary, 9- history of alcohol abuse, tubal or male factor infertility, 10- no desire to conceive.

Palomba 2007 *(Continued)*

	Myoma characteristics: 1- three or more uterine fibroids, 2-fibroids with a main diameter less than 3 cm, 3- fibroids with a mean diameter of more than 10 cm, 4- hypoechoic or calcified fibroids, 5- presence of submucosal fibroids, 6- uterine cavity distortion diagnosed by hysteroscopy, 7- other uterine or adnexal abnormalities at ultrasound, 8- endometrial hyperplasia or atypia, 9- abnormal cervical smear.
Interventions	Laparoscopic myomectomy or myomectomy by minilaparotomy
Outcomes	1- Cumulative pregnancy rate: calculated as the ratio between number of pregnant women and total number of patients studied. 2- Cumulative live birth rate: calculated as women with a baby alive over the total number of pregnant women. 3- Miscarriage rate: defined as the ratio between number of miscarriages during the first 12 weeks of gestation and total pregnancies. 4- Pregnancy rate and live birth rates per cycle, defined as the ratio between number of pregnancies and live births, respectively, and the total number of cycles studied.
Notes	No power calculation. Only the subgroup of patients with unexplained infertility were included in the meta-analysis. Follow-up period: 12 months. Those obtaining pregnancy within 12 months were followed up for another 9 months Funding: none stated Conflict of interest: none stated Study dates: 2002-2003 Trial registration number: unknown The study was approved by the Institutional Review Board (IRB) of the University “Magna Graecia” of Catanzaro, Italy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation performed using online software (www.randomization.it)
Allocation concealment (selection bias)	Low risk	The random allocation sequence was concealed in a closed and dark-coloured envelope until immediately prior to surgery
Blinding of participants and personnel (Performance bias) All outcomes	Low risk	Due to the nature of the intervention, personnel could not be blinded. Furthermore, participants could not be blinded to which intervention they received as the surgical incisions varied between interventions. Therefore, performance bias was not considered a source of bias in this study,
Blinding of outcome assessors (Detection bias) All outcomes	Unclear risk	It remains unclear whether outcome assessors were blinded when analysing results (detection bias)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all patients who started the study

Palomba 2007 *(Continued)*

Selective reporting (reporting bias)	Low risk	All specified outcomes reported in the results section
Other bias	Low risk	No evidence of other bias

Roy 2017

Methods	Randomised controlled trial
Participants	68 participants Monopolar n =34 Bipolar n =34 Participants infertile women with submucous fibroids The inclusion criteria were the following: (1) submucous myoma of Type 0 FIGO PALM COEIN classification diagnosed during outpatient hysteroscopy, (2) history of infertility, (3) age less than 35 years, (5) written informed consent, and (6) normal semen parameters of the husband The exclusion criteria were the following: (1) patients with any other known cause of infertility were excluded from the study, (2) the presence of fibroid other than Type 0 FIGO PALM COEIN classification, (3) fibroid size more than 3 cm, or (4) more than 2 myomas
Interventions	Hysteroscopic myomectomy using monopolar or bipolar resectoscope
Outcomes	Primary outcomes: pregnancy-related indicators (improvement in menstrual symptoms, clinical pregnancy rate, abortion rate, live birth rate/ongoing pregnancy rate > 30 weeks) Secondary outcomes: operative parameters, harmful outcomes related to the procedure, and comparison of improvement levels in the menstrual pattern after surgery between the two groups
Notes	Authors were contacted regarding gathering data for our primary outcome live birth rate. Live birth rate is dual reported with ongoing pregnancy rate > 30 weeks in the article. Authors did not respond to our attempts to contact them. Power calculation was performed but not adhered to. Follow-up period: a minimum of 12 months (no average or maximum follow-up period was stated) Funding: authors state no funding given Conflict of interest: authors state no conflict of interest Study dates: 2012-2016 Trial registration number: unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised into two groups using Epi-Info version 7.0 software
Allocation concealment (selection bias)	Low risk	Allocation sequence was concealed and stapled envelopes were handed to the statistician

Roy 2017 *(Continued)*

Blinding of participants and personnel (Performance bias) All outcomes	Low risk	Participants were blinded to which intervention they received. Due to the nature of the intervention, personnel could not be blinded. Therefore, performance bias was not considered a source of bias in this study,
Blinding of outcome assessors (Detection bias) All outcomes	Unclear risk	It remains unclear whether outcome assessors were blinded when analysing results (detection bias)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all participants that started the study
Selective reporting (reporting bias)	High risk	Four of five prespecified reproductive outcomes were reported on
Other bias	Low risk	No evidence of other bias

Seracchioli 2000

Methods	Randomised controlled trial
Participants	131 participants Laparoscopy n = 56 Laparotomy n = 59 Participants infertile women with at least one myoma greater than 5 cm. Inclusion criteria: infertile women with infertility and fibroids. Exclusion criteria: 1- pedunculated fibroids 2- uterine size above the umbilicus 3-more than three fibroids > 5 cm in diameter 4- associated other causes of infertility such as tubal or male factor 5- uterine cavity abnormalities.
Interventions	Laparoscopic myomectomy or myomectomy at laparotomy
Outcomes	Surgical outcomes: 1- mean operative time 2- average postoperative drop in haemoglobin 3- Incidence of postoperative pyrexia 4- average postoperative hospital stay. Fertility outcomes: 1- clinical pregnancy rate 2- miscarriage rate 3- ongoing clinical pregnancy 4- preterm delivery rate 5- caesarean section rate.
Notes	No power calculation Follow-up period: authors allowed for 6 months after surgical resection before trying for pregnancy. After this, authors state a minimum follow-up period of 12 months. (Group 1 mean: 32.4+/-18.5 months, Group 2: 30.6+/-16.9 months) Funding: none stated Conflict of interest: none stated Study dates: 1991-1998 Trial registration number: unknown

Seracchioli 2000 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by random number generation
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (Performance bias) All outcomes	Low risk	Due to the nature of the intervention, personnel could not be blinded. Furthermore, participants could not be blinded as surgical scars varied between interventions. Therefore, performance bias was not considered a source of bias in this study,
Blinding of outcome assessors (Detection bias) All outcomes	Unclear risk	It remains unclear whether outcome assessors were blinded when analysing results (detection bias)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all patients who started the study
Selective reporting (reporting bias)	Low risk	All specified outcomes reported in the results section
Other bias	Low risk	No evidence of other bias

FSH: follicle stimulating hormone; IM: intramural; SM: submucous; SS: subserous.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bernard 2000	Retrospective observational study
Bulletti 1999	Prospective observational study
Bulletti 2004	Non randomised study
Campo 2003	Prospective observational study
Chang 2011	1- Non-randomised study 2- Infertility not an inclusion criterion
Chatterjee 2012	Retrospective observational study
Chong 1988	Retrospective observational study
Darai 1997	Retrospective observational study
Dubuisson 2000	Retrospective observational study
Fauconnier 2000	Retrospective observational study

Study	Reason for exclusion
Fernandez 2001	Retrospective observational study
Gatti 1989	Retrospective observational study
Gehlbach 1993	Retrospective observational study
Giatras 1999	Retrospective observational study
Kim 2013	Retrospective observational study
Kramer 2016	Randomised controlled trial but intervention assessed is not within the scope of this review
Li 1999	Retrospective observational study
Litta 2014	Retrospective observational study
Malzoni 2003	Retrospective observational study
Narayan 1994	Retrospective observational study
Ribeiro 1999	Retrospective observational study
Rossetti 2001	Retrospective observational study
Saleh 2018	Prospective observational study
Sato 2018	Conference abstract Retrospective observational study
Seyam 2015	Prospective controlled study, not randomised
Shokeir 2010	This article was retracted in 2011 by the editors of Fertility and Sterility as it duplicates parts of a paper in Hum Reprod 2005;20:1632-5
Spies 2010	Prospective study not randomised
Sudik 1996	Comparative retrospective non-randomised study
Ubaldi 1995	Retrospective observational study
Varasteh 1999	Retrospective observational study
Vercellini 1999a	Retrospective observational study
Vercellini 1999b	Retrospective observational study
Wang 2013	Prospective uncontrolled study
Wang 2016	Retrospective observational study
Wen 2018	Prospective study not randomised
Yarali 2002	Retrospective observational study

Characteristics of ongoing studies *[ordered by study ID]*

NCT03143114

Trial name or title	Effect of myomectomy for intramural myoma on fertility outcomes in infertile women
Methods	Randomised controlled trial
Participants	100 participants (estimated) Criteria Inclusion Criteria: Infertility for at least one year. Presence of intramural myoma. Absence of any other cause of infertility as revealed by basic infertility work up including laparoscopy. Exclusion Criteria: Age is < 20 or > 33 years. Symptomatic fibroid causing pelviabdominal swelling. Presence of > 2 myomas. Presence of a coexisting another type of myoma other than intramural myoma (e.g. submucosal, subserosal, cervical or ligamentary myoma). Presence of any other cause of infertility.
Interventions	Group 1: Myomectomy by laparotomy Group 2: Conservative management
Outcomes	Primary outcome: Clinical pregnancy rate [Time Frame: 6-8 weeks gestational age] Number of clinical pregnancies (defined as presence of at least one intrauterine gestational sac with fetal pole and cardiac activity on TVS scan at 6-8 weeks gestational age) divided by the number of women Secondary outcome: Miscarriage rate [Time Frame: 12 weeks gestational age] Number of first trimester miscarriages (before 12 weeks gestational age) divided by the number of clinical pregnancies
Starting date	First posted 8 May 2017 Last updated 30 October 2018
Contact information	wrefaie@yahoo.com
Notes	https://clinicaltrials.gov/show/NCT03143114 Authors were contacted regarding preliminary data but no response was received

NCT03796130

Trial name or title	Does myomectomy for intramural fibroid improve ART outcome?

NCT03796130 *(Continued)*

Methods	Randomised controlled trial
Participants	80 participants (estimated) This study will include women who have intramural myomas ranging from 3-5 cm
Interventions	Group 1: Myomectomy will be performed before ART Group 2: Women will have their trial of ART without myomectomy
Outcomes	Primary outcome: Ongoing pregnancy rate [Time Frame: 3 months after embryo transfer] Secondary outcomes: 1. Implantation rate [Time Frame: 15 days after embryo transfer] 2. Clinical pregnancy rate [Time Frame: 5 weeks after embryo transfer]
Starting date	01/12/19
Contact information	eman_elgindy2013@hotmail.com
Notes	https://clinicaltrials.gov/show/NCT03796130 Authors were contacted regarding preliminary data but no response was received

ART: assisted reproductive technology

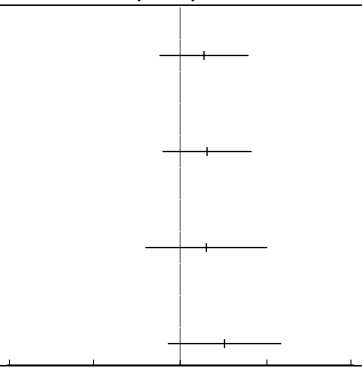
DATA AND ANALYSES

Comparison 1. Myomectomy versus no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical pregnancy rate	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Intramural	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Submucous	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Intramural/Subserous	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Intramural/Submucous	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Miscarriage rate	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Intramural	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Submucous	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Intramural/Subserous	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Intramural/Submucous	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

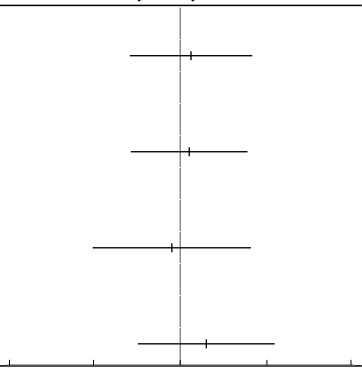
Analysis 1.1. Comparison 1 Myomectomy versus no intervention, Outcome 1 Clinical pregnancy rate.

Study or subgroup	Myomectomy n/N	No intervention n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.1.1 Intramural				
Casini 2006	13/23	9/22		1.88[0.57,6.14]
1.1.2 Submucous				
Casini 2006	13/30	6/22		2.04[0.62,6.66]
1.1.3 Intramural/Subserous				
Casini 2006	6/17	3/14		2[0.4,10.09]
1.1.4 Intramural/Submucous				
Casini 2006	8/22	3/20		3.24[0.72,14.57]



Analysis 1.2. Comparison 1 Myomectomy versus no intervention, Outcome 2 Miscarriage rate.

Study or subgroup	Myomectomy n/N	No intervention n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.2.1 Intramural				
Casini 2006	4/23	3/22		1.33[0.26,6.78]
1.2.2 Submucous				
Casini 2006	5/30	3/22		1.27[0.27,5.97]
1.2.3 Intramural/Subserous				
Casini 2006	2/17	2/14		0.8[0.1,6.54]
1.2.4 Intramural/Submucous				
Casini 2006	4/22	2/20		2[0.32,12.33]



Comparison 2. Laparoscopic myomectomy versus myomectomy by laparotomy or mini laparotomy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate	2	177	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.42, 1.50]
2 Preterm delivery rate	2	177	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.11, 4.29]
3 Clinical pregnancy rate	2	177	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.52, 1.78]
4 Ongoing pregnancy rate	1	115	Odds Ratio (M-H, Fixed, 95% CI)	1.61 [0.26, 10.04]
5 Miscarriage rate	2	177	Odds Ratio (M-H, Fixed, 95% CI)	1.25 [0.40, 3.89]

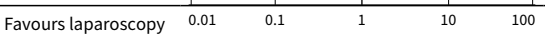
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Caesarean section rate	2	177	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.34, 1.39]

Analysis 2.1. Comparison 2 Laparoscopic myomectomy versus myomectomy by laparotomy or mini laparotomy, Outcome 1 Live birth rate.

Study or subgroup	Laparoscopy n/N	Laparotomy n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Palomba 2007	7/30	6/32		20.84%	1.32[0.39,4.5]
Seracchioli 2000	20/56	27/59		79.16%	0.66[0.31,1.39]
Total (95% CI)	**86**	**91**		**100%**	**0.8[0.42,1.5]**
Total events: 27 (Laparoscopy), 33 (Laparotomy)					
Heterogeneity: Tau^2=0; Chi^2=0.9, df=1(P=0.34); I^2=0%					
Test for overall effect: Z=0.7(P=0.48)					

Analysis 2.2. Comparison 2 Laparoscopic myomectomy versus myomectomy by laparotomy or mini laparotomy, Outcome 2 Preterm delivery rate.

Study or subgroup	Favours laparoscopy n/N	Laparotomy n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Palomba 2007	1/30	1/32		32.84%	1.07[0.06,17.89]
Seracchioli 2000	1/56	2/59		67.16%	0.52[0.05,5.88]
Total (95% CI)	**86**	**91**		**100%**	**0.7[0.11,4.29]**
Total events: 2 (Favours laparoscopy), 3 (Laparotomy)					
Heterogeneity: Tau^2=0; Chi^2=0.15, df=1(P=0.7); I^2=0%					
Test for overall effect: Z=0.39(P=0.7)					

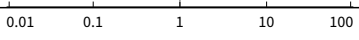


Analysis 2.3. Comparison 2 Laparoscopic myomectomy versus myomectomy by laparotomy or mini laparotomy, Outcome 3 Clinical pregnancy rate.

Study or subgroup	Laparoscopy n/N	Laparotomy n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Palomba 2007	8/30	8/32		27.56%	1.09[0.35,3.4]
Seracchioli 2000	30/56	33/59		72.44%	0.91[0.44,1.9]
Total (95% CI)	**86**	**91**		**100%**	**0.96[0.52,1.78]**
Total events: 38 (Laparoscopy), 41 (Laparotomy)					
Heterogeneity: Tau^2=0; Chi^2=0.07, df=1(P=0.79); I^2=0%					
Test for overall effect: Z=0.13(P=0.89)					

Analysis 2.4. Comparison 2 Laparoscopic myomectomy versus myomectomy by laparotomy or mini laparotomy, Outcome 4 Ongoing pregnancy rate.

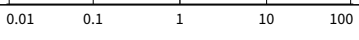
Study or subgroup	Laparoscopy n/N	Laparotomy n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Seracchioli 2000	3/56	2/59		100%	1.61[0.26,10.04]
Total (95% CI)	**56**	**59**		**100%**	**1.61[0.26,10.04]**
Total events: 3 (Laparoscopy), 2 (Laparotomy)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.51(P=0.61)					



Favours laparotomy — Favours laparoscopy

Analysis 2.5. Comparison 2 Laparoscopic myomectomy versus myomectomy by laparotomy or mini laparotomy, Outcome 5 Miscarriage rate.

Study or subgroup	Laparoscopy n/N	Laparotomy n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Palomba 2007	1/30	2/32		34.98%	0.52[0.04,6.02]
Seracchioli 2000	6/56	4/59		65.02%	1.65[0.44,6.19]
Total (95% CI)	**86**	**91**		**100%**	**1.25[0.4,3.89]**
Total events: 7 (Laparoscopy), 6 (Laparotomy)					
Heterogeneity: Tau^2=0; Chi^2=0.67, df=1(P=0.41); I^2=0%					
Test for overall effect: Z=0.39(P=0.7)					



Favours laparoscopy — Favours laparotomy

Analysis 2.6. Comparison 2 Laparoscopic myomectomy versus myomectomy by laparotomy or mini laparotomy, Outcome 6 Caesarean section rate.

Study or subgroup	Laparoscopy n/N	Laparotomy n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Palomba 2007	5/30	4/32		17.04%	1.4[0.34,5.8]
Seracchioli 2000	13/56	21/59		82.96%	0.55[0.24,1.24]
Total (95% CI)	**86**	**91**		**100%**	**0.69[0.34,1.39]**
Total events: 18 (Laparoscopy), 25 (Laparotomy)					
Heterogeneity: Tau^2=0; Chi^2=1.26, df=1(P=0.26); I^2=20.74%					
Test for overall effect: Z=1.03(P=0.3)					

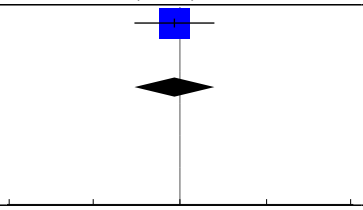
Favours laparoscopy — Favours laparotomy

Comparison 3. Monopolar versus bipolar resectoscope use in hysteroscopic myomectomy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate/ongoing pregnancy rate	1	68	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.30, 2.50]
2 Clinical pregnancy rate	1	68	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.33, 2.36]
3 Miscarriage rate	1	68	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.19, 5.34]

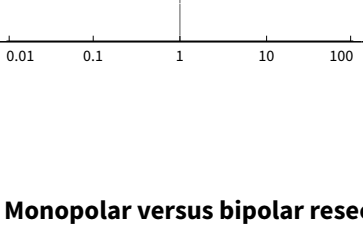
Analysis 3.1. Comparison 3 Monopolar versus bipolar resectoscope use in hysteroscopic myomectomy, Outcome 1 Live birth rate/ongoing pregnancy rate.

Study or subgroup	Monopolar resectoscope n/N	Bipolar resectoscope n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Roy 2017	9/34	10/34		100%	0.86[0.3,2.5]
Total (95% CI)	**34**	**34**		**100%**	**0.86[0.3,2.5]**
Total events: 9 (Monopolar resectoscope), 10 (Bipolar resectoscope)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.27(P=0.79)					



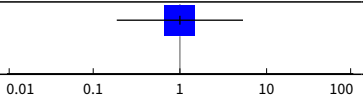
Analysis 3.2. Comparison 3 Monopolar versus bipolar resectoscope use in hysteroscopic myomectomy, Outcome 2 Clinical pregnancy rate.

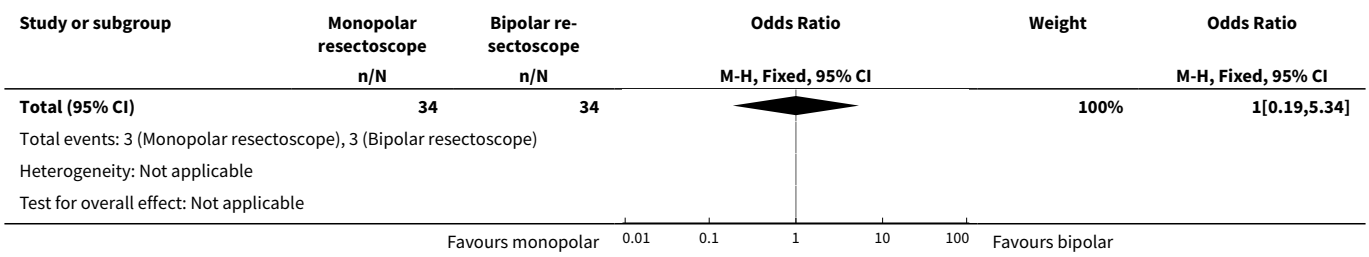
Study or subgroup	Monopolar resectoscope n/N	Bipolar resectoscope n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Roy 2017	12/34	13/34		100%	0.88[0.33,2.36]
Total (95% CI)	**34**	**34**		**100%**	**0.88[0.33,2.36]**
Total events: 12 (Monopolar resectoscope), 13 (Bipolar resectoscope)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.25(P=0.8)					



Analysis 3.3. Comparison 3 Monopolar versus bipolar resectoscope use in hysteroscopic myomectomy, Outcome 3 Miscarriage rate.

Study or subgroup	Monopolar resectoscope n/N	Bipolar resectoscope n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Roy 2017	3/34	3/34		100%	1[0.19,5.34]





APPENDICES

Appendix 1. Cochrane Gynaecology and Fertility Group's specialised register search strategy

Searched 26 February 2019

Procite platform

Keywords CONTAINS "fibroid" or "Leiomyoma*" or "myoma" or "myomas" or "uterine leiomyomas" or "uterine myoma" or "uterine myomas" or "uterine fibroids" or "fibroids" or Title CONTAINS "fibroid" or "Leiomyoma*" or "myoma" or "myomas" or "uterine leiomyomas" or "uterine myoma" or "uterine myomas" or "uterine fibroids" or "fibroids"

AND

Keywords CONTAINS "surgery" or "surgery-gynaecological" or "surgery vs medicine" or "Surgical" or "*Surgical-Procedures,-Laparoscopic" or "surgical treatment" or "myomectomy" or "laparoscopic myomectomy" or "laparoscopic procedure" or "laparoscopic surgical treatment" or "laparotomy" or "hysteroscopic surgery" or "hysteroscopy" or "microlaparoscopy" or "microsurgery" or Title CONTAINS "surgery" or "surgery-gynaecological" or "surgery vs medicine" or "Surgical" or "*Surgical-Procedures,-Laparoscopic" or "surgical treatment" or "myomectomy" or "laparoscopic myomectomy" or "laparoscopic procedure" or "laparoscopic surgical treatment" or "laparotomy" or "hysteroscopic surgery" or "hysteroscopy" or "microlaparoscopy" or "microsurgery"

(408 records)

Appendix 2. CENTRAL via Cochrane Central Register of Studies Online (CRSO) search strategy

Searched 26 February 2019

Web platform

#1 MESH DESCRIPTOR Leiomyoma EXPLODE ALL TREES 584

#2 MESH DESCRIPTOR Myoma EXPLODE ALL TREES 24

#3 (Leiomyoma* or fibroid*):TI,AB,KY 1091

#4 (uter* adj5 fibroma*):TI,AB,KY 13

#5 (myom* or hysteromyom* or fibromyom*):TI,AB,KY 1560

#6 #1 OR #2 OR #3 OR #4 OR #5 2125

#7 MESH DESCRIPTOR Gynecologic Surgical Procedures EXPLODE ALL TREES 4028

#8 MESH DESCRIPTOR Laparoscopy EXPLODE ALL TREES 5124

#9 MESH DESCRIPTOR Hysteroscopy EXPLODE ALL TREES 363

#10 MESH DESCRIPTOR Uterine Myomectomy EXPLODE ALL TREES 46

#11 MESH DESCRIPTOR Microsurgery EXPLODE ALL TREES 614

#12 MESH DESCRIPTOR Laparotomy EXPLODE ALL TREES 701

#13 (microsurg* or surg*):TI,AB,KY 173032

#14 (Laparoscop* or minilaparoscop*):TI,AB,KY 13570

#15 Hysteroscop* :TI,AB,KY 1037

#16 myomectom*:TI,AB,KY 535

#17 (Laparotom* or minilaparotom*):TI,AB,KY 2489

#18 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 177578

#19 #6 AND #18 1158

#20 2012 TO 2019:YR 514326

#21 01/01/2012 TO 26/02/2019:CD 643072

#22 #20 OR #21 643083

#23 #19 AND #22 673

Appendix 3. MEDLINE search strategy

Searched from 1946 to 26 February 2019

OVID platform

1. exp Leiomyoma/ (20114)

2. (Leiomyoma$ or fibroid$).tw. (18116)

3. (uter$ adj5 fibroma$).tw. (405)

4. exp Myoma/ (2716)

5. (myom$ or hysteromyom$ or fibromyom$).tw. (23071)

6. or/1-5 (44362)

7. exp Gynecologic Surgical Procedures/ (78898)

8. microsurg$.tw. (23975)

9. exp hysteroscopy/ or exp laparoscopy/ (94599)

10. exp Uterine Myomectomy/ (742)

11. exp Microsurgery/ (32013)

12. exp Laparotomy/ (18164)

13. (Laparoscop$ or minilaparoscop$).tw. (115957)

14. Hysteroscop$.tw. (6391)

15. surg$.tw. (1760957)

16. myomectom$.tw. (3318)

17. Laparotom$.tw. (46459)

18. minilaparotom$.tw. (1030)

19. or/7-18 (1906437)

20. 6 and 19 (14784)

21. randomized controlled trial.pt. (476544)

22. controlled clinical trial.pt. (92921)

23. randomized.ab. (435206)

24. placebo.tw. (200882)

25. clinical trials as topic.sh. (186073)

26. randomly.ab. (305887)

27. trial.ti. (194540)

28. (crossover or cross-over or cross over).tw. (79266)

29. or/21-28 (1227748)

30. exp animals/ not humans.sh. (4549808)

31. 29 not 30 (1127992)

32. 20 and 31 (873)

Appendix 4. Embase search strategy

Searched from 1980 to 26 February 2019

OVID platform

1. exp leiomyoma/ or exp uterus myoma/ (29328)

2. (Leiomyoma$ or fibroid$).tw. (24016)

3. (uter$ adj5 fibroma$).tw. (345)

4. (myom$ or hysteromyom$ or fibromyom$).tw. (28853)

5. or/1-4 (54814)

6. exp Gynecologic Surgical Procedures/ or exp uterus surgery/ (134198)

7. microsurg$.tw. (27861)

8. exp microsurgery/ or exp myotomy/ (37988)

9. exp Laparotomy/ (70673)

10. (Laparoscop$ or minilaparoscop$).tw. (184220)

11. exp Laparoscopy/ (146549)

12. Hysteroscop$.tw. (10932)

13. exp hysteroscopy/ (11137)

14. surg$.tw. (2244163)

15. exp Uterine Myomectomy/ (6335)

16. myomectom$.tw. (5791)

17. Laparotom$.tw. (59834)

18. minilaparotom$.tw. (1307)

19. or/6-18 (2451389)

20. Clinical Trial/ (944597)

21. Randomized Controlled Trial/ (533054)

22. exp randomization/ (81333)

23. Single Blind Procedure/ (33971)

24. Double Blind Procedure/ (155315)

25. Crossover Procedure/ (58216)

26. Placebo/ (316874)

27. Randomi?ed controlled trial$.tw. (197224)

28. Rct.tw. (31346)

29. random allocation.tw. (1859)

30. randomly allocated.tw. (31715)

31. allocated randomly.tw. (2398)

32. (allocated adj2 random).tw. (799)

33. Single blind$.tw. (22115)

34. Double blind$.tw. (188192)

35. ((treble or triple) adj blind$).tw. (902)

36. placebo$.tw. (279419)

37. prospective study/ (501549)

38. or/20-37 (1982692)

39. case study/ (59090)

40. case report.tw. (363254)

41. abstract report/ or letter/ (1049465)

42. or/39-41 (1462477)

43. 38 not 42 (1932607)

44. 5 and 19 and 43 (2735)

Appendix 5. PsycINFO search strategy

Searched from 1806 to 26 February 2019

OVID platform

1. (Leiomyoma$ or fibroid$).tw. (77)

2. (uter$ adj5 fibroma$).tw. (4)

3. (myoma$ or hysteromyoma$ or fibromyom$).tw. (29)

4. or/1-3 (109)

5. exp surgery/ (54923)

6. microsurg$.tw. (232)

7. Laparoscop$.tw. (468)

8. Hysteroscop$.tw. (17)

9. surg$.tw. (46504)

10. myomectom$.tw. (11)

11. Laparotom$.tw. (158)

12. or/5-11 (84377)

13. 4 and 12 (43)

14. random.tw. (54555)

15. control.tw. (419970)

16. double-blind.tw. (21948)

17. clinical trials/ (11241)

18. placebo/ (5205)

19. exp Treatment/ (725477)

20. or/14-19 (1134175)

21. 13 and 20 (31)

Appendix 6. CINAHL search strategy

Searched from 1961 to 26 February 2019

EBSCO platform

#	Query	Results
S32	S19 AND S31	322
S31	S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30	1,304,565
S30	TX allocat* random*	9,874
S29	(MH "Quantitative Studies")	21,853
S28	(MH "Placebos")	11,144
S27	TX placebo*	55,420
S26	TX random* allocat*	9,874
S25	(MH "Random Assignment")	53,511
S24	TX randomi* control* trial*	163,780
S23	TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))	1,003,357
S22	TX clinic* n1 trial*	238,860
S21	PT Clinical trial	86,752
S20	(MH "Clinical Trials+")	254,336

(Continued)

S19	S6 AND S18	2,222
S18	S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17	47,294
S17	TX minilaparotom*	116
S16	TX Laparotom*	6,681
S15	TX myomectom*	1,051
S14	(MM "Surgery, Laparoscopic+")	4,407
S13	TX Hysteroscop*	2,058
S12	(MM "Hysteroscopy")	872
S11	TX Laparoscop* or TX minilaparoscop*	30,260
S10	(MM "Laparotomy")	1,092
S9	(MM "Microsurgery+")	1,614
S8	TX microsurg*	3,913
S7	(MM "Surgery, Gynecologic+")	8,805
S6	S1 OR S2 OR S3 OR S4 OR S5	6,654
S5	TX myom* or TX hysteromyom* or TX fibromyom*	2,989
S4	(MM "Myoma+")	213
S3	TX uter* N5 fibroma*	21
S2	TX Leiomyoma* or TX fibroid*	4,606
S1	(MM "Leiomyoma")	2,684

Appendix 7. Data extraction form

Data extraction form	Findings
Title	
Authors	
Journal	
Year	
DOI	

(Continued)

Location
Study design
Participants (plus inclusion and exclusion criteria)
Intervention
Comparison
Outcomes
Other
Risk of bias

WHAT'S NEW

Date	Event	Description
6 June 2019	New citation required but conclusions have not changed	The addition of one new included study has not changed the conclusions of this review.
6 June 2019	New search has been performed	New study included: Roy 2017 Eleven studies excluded: Spies 2010; Chatterjee 2012; Kim 2013; Wang 2013; Litta 2014; Seyam 2015; Kramer 2016; Wang 2016; Saleh 2018; Sato 2018; Wen 2018; Two ongoing clinical trials NCT03143114; NCT03796130. Primary and secondary outcome measures have been updated and modified. Live birth rate remained the primary effectiveness measure. Preterm delivery was promoted to a primary outcome as the primary safety measure as it is the leading cause of neonatal mortality. Methods sections updated to reflect CGF policy e.g. ensuring the denominator for the primary analyses is per woman randomised.

HISTORY

Protocol first published: Issue 4, 2002
Review first published: Issue 3, 2006

Date	Event	Description
12 September 2012	New citation required but conclusions have not changed	There remains insufficient evidence for performing myomectomy to improve fertility.
29 August 2012	New search has been performed	Summary of findings tables generated from GRADE software and incorporated in review.

Date	Event	Description
		2 new studies included: Casini 2006; Palomba 2007; 3 studies excluded: Bulletti 2004; Chang 2011; Shokeir 2010. Primary and secondary outcome measures have been updated and modified. The primary outcome measure is live birth rate, while secondary outcomes include: ongoing pregnancy rate, miscarriage rate, clinical pregnancy rate, caesarean section and preterm delivery rates.
17 November 2010	New search has been performed	Updated searches performed
6 November 2008	Amended	Converted to new review format.
15 May 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

GR and MM extracted and entered the data and wrote the review. AH and YC acted as review authors. Both AH and YC proof-read and commented on the review.

DECLARATIONS OF INTEREST

MM, GR, and YC declare no known conflicts of interest. AH has received grant funding from the MRC, NIHR, CSO, Wellbeing of Women, Roche Diagnostics, Astra Zeneca and Ferring, and is Chair of RCOG Academic Board, ESHRE National Representative for the UK, WES Ambassador, SEUD Board Member, Past Chair of ESHRE Special Interest Group Endometriosis, Member of NICE and ESHRE Endometriosis Guideline Groups, Trustee and Medical Advisor to Endometriosis UK, Medical Advisor to Pelvic Pain Support Network, and Deputy Editor in chief of Human Reproduction Open. AH's institution has received consultancy fees from Roche Diagnostics, AbbVie, Nordic Pharma and Ferring for work carried out on their behalf.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Primary and secondary outcome measures have been updated and modified. In the previous review, only one primary outcome existed (Primary effectiveness measure: Live birth rate). Preterm delivery rate was promoted from a secondary outcome to a primary outcome as the primary safety measure as it is the leading cause of neonatal mortality. Secondary outcomes are clinical pregnancy rate, ongoing pregnancy rate, miscarriage rate, clinical pregnancy rate and caesarean section. Methods sections have been updated to reflect Cochrane Gynaecology and Fertility policy such as ensuring the denominator for the primary analyses is per woman randomised.

INDEX TERMS

Medical Subject Headings (MeSH)

Abortion, Spontaneous [epidemiology]; Cesarean Section [statistics & numerical data]; Infertility, Female [etiology] [*surgery]; Leiomyomatosis [complications] [*surgery]; Live Birth [epidemiology]; Pregnancy Rate; Randomized Controlled Trials as Topic; Uterine Myomectomy [*methods]; Uterine Neoplasms [complications] [*surgery]

MeSH check words

Female; Humans; Pregnancy